84. The optimally effective patient-specific therapeutic dose of claim 19 wherein the radiopharmaceutical is an ^{131}I-labeled anti-B1 antibody.

REMARKS

Amendments

Claims 1-2, 4-20, 22-24, and 83-84 are pending in the application. Claims 3 and 21 have been cancelled. Claims 1, 18, 19, 20, and 84 have been amended.

Further, the specification has been amended in the section entitled "Brief Description of the Drawings" to refer to each figure separately.

35 U.S.C. §112, second paragraph

Several claims were rejected under the second paragraph of §112. Applicant requests that the rejection be withdrawn.

The Examiner questions why the clearance profile is not itemized in the final equation of claim 1 or of claim 19. Notably, however, residence time is included in the final equation. According to the invention, residence time of the tracer dose is correlated to the clearance profile. This language is in claims 1 and 19. Page 22 of the specification further expands upon this aspect of the invention.

Claims 1 and 19 had been previously amended to bring them in conformity with the language of original claim 20 and to expand upon the description of determining residence time of an administered tracer dose. The precise language for the step of "determining residence time of an administered tracer dose" makes evident that a tracer dose is present so that its residence time can be gleaned from the patient according to the invention. Claims 1 and 10 clearly define what Applicant regards as his invention and therefore Applicant believes that an additional step need not be enumerated in such claims.

The Examiner has stated that it is unclear whether the "optimally effective dose" is equal to the "therapeutic dose" and suggests remedies. Applicant submits that the optimally effective dose to which reference is made in the preamble of claim 1 is a therapeutic dose and points to the language of claim 1 specifying the step of "*establishing*

the optimally effective dose of the radiopharmaceutical for the patient *by solving for* therapeutic dose in the following equation . . ." (emphasis added). To make this clearer, however, the word "therapeutic" has been added to the preamble of claim 1 so that it is evident that the method is directed to establishing a"patient-specific optimally effective therapeutic dose" for administration to the patient. It is believed that claim 19 needs nothing further in this regard.

The Examiner has questioned how maximum effective mass would be determined by a dose escalation study, but Applicant suggests that this question simply results from a misreading of claim 2. Claim 2 refers to maximum tolerated dose, an end point well-known in the art for dose escalation studies. Dose escalation studies may provide a variety of information, including the highest tolerable dose administrable, a sense of the activity-time curve shape for the radiopharmaceutical, the clearance profile, and other information. It is not necessary that the same study be used to provide the parameters of both claims 2 and 7, but neither is it prohibited.

Claim 3 has been cancelled.

Claims 10, 13, 15, and 18 are further claims expanding upon the step of determining the residence time for the radiopharmaceutical. Claim 1 includes the step of determining residence time of an administered dose of the radiopharmaceutical or analog thereof, as discussed above, and thus, its dependent claims 10, 13, 15, and 18, expand upon how that step of claim 1 may be performed.

Claim 18 has been amended as suggested by the Examiner.

Claim 84 has been amended to correct the improper reference to the method of claim 19.

35 U.S.C. §102

The pending claims have been subjected to a rejection under 102(b) as being anticipated by Wahl, *et al.*, WO 96/34632. Applicant submits, however, that the present invention is distinguishable therefrom.

The method of claim 1 may be performed for a variety of radiopharmaceuticals, including those that follow a complex clearance profile. Radiopharmaceuticals are

described in great length at pages 4-6 of the specification of the instant application. As described on page 11 of the specification, the clearance profile may be dependent upon factors such as specificity and affinity of the radiopharmaceutical to its target, the size of the radiopharmaceutical, and its origin. According to the present invention, weight is given to the nature of the clearance profile for the radiopharmaceutical that will eventually be administered to the patient for therapy. Determining the clearance profile is a factor in Applicant's method of establishing the optimally effective patient-specific therapeutic dose. Knowledge of the pattern of radioactivity clearance for a particular radiopharmaceutical, together with other factors, is important to the inventive method, as discussed further at page 27, lines 4-6. The phrase "determining a clearance profile" is included in the language of claim 1 and serves to distinguish the claim from the teachings of the Wahl reference. Claim 19 includes similar language.

Additionally, Applicant has amended claim 20 to incorporate language of dependent claim 21. Claim 20 now specifies that the clearance profile for the radiopharmaceutical is determined. Claim 21 has been cancelled.

Applicant requests that the rejection of the pending claims based on the Wahl reference be withdrawn.

Claim 19 stands rejected as anticipated by Order, Reference D11. Applicant has made an amendment to claim 19, as set forth above, to more precisely define the scope of the invention. Such amendment also serves to distinguish Order.

Notably, claim 19 has been amended to further clarify that the optimally effective dose of the invention is *patient-specific*. It is evident from the specification that the nature of the end product is tailored to account for individual patient variances and is therefore patient-specific. Order reports on the "toxicity and possible therapeutic efficacy of radiolabelled antibodies of radiolabelled antibodies that were administered at 50 and 100 millicurie doses. . ." (abstract). Thus, the end product of the process described in claim 19 is patentably distinct from anything described in Order. Clearly, no account has been made in the prior art for adjusting the therapeutic dose as a consequence of how a particular patient clears a given antibody or other pharmaceutical, or any other individual variances. Applicant requests that the rejection based on the Order reference be removed.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited. The Examiner is invited to telephone the undersigned representative of the Applicant at (415) 693-2120 if any issues remain.

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Attachment

Respectfully submitted,
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Version with markings to show changes made

1. (Three Times Amended) A method of establishing a patient-specific optimally effective therapeutic dose for administration of a radiopharmaceutical to a patient, the method comprising:

determining a maximum tolerated dose for the radiopharmaceutical;

determining a desired total body dose of the radiopharmaceutical for the patient;

determining a clearance profile for the radiopharmaceutical or a radiopharmaceutical analog;

determining the patient's mass and maximum effective mass;

selecting the lower of the patient's mass and maximum effective mass;

determining activity hours for the radiopharmaceutical or radiopharmaceutical analog based on the lower of the patient's mass or maximum effective mass and the desired total body dose;

determining residence time of an administered tracer dose of the radiopharmaceutical or the radiopharmaceutical analog in the whole body of the patient, the residence time being correlated to the clearance profile; and

establishing the optimally effective dose of the radiopharmaceutical for the patient by solving for therapeutic dose in the following equation:

$$\text{therapeutic dose} = \frac{\text{Activity Hours}}{\text{Residence time}} \times \frac{\text{desired total body dose}}{\text{maximum tolerated dose.}}$$

18. (Amended) The method of claim 1, wherein the step of determining the residence time for the radiopharmaceutical comprises:

making measurements of radioactivity in the whole body of the patient at each of a number of time points, generating an activity-time curve, and using the trapezoidal rule or Simpson's rule to determine the residence time.

19. (Twice Amended) An optimally effective patient-specific therapeutic dose of a radiopharmaceutical for administration to a patient, said optimally effective therapeutic dose determined by the method comprising:

determining a maximum tolerated dose for the radiopharmaceutical;

determining a desired total body dose of the radiopharmaceutical for the patient;

determining a clearance profile for the radiopharmaceutical or a radiopharmaceutical analog;

determining the patient's mass and maximum effective mass;

selecting the lower of the patient's mass and maximum effective mass;

determining activity hours for the radiopharmaceutical or radiopharmaceutical analog based on the lower of the patient's mass or maximum effective mass and the desired total body dose;

determining residence time of an administered tracer dose of the radiopharmaceutical or the radiopharmaceutical analog in the whole body of the patient, the residence time being correlated to the clearance profile; and

establishing the optimally effective patient-specific dose of the radiopharmaceutical for the patient by solving for therapeutic dose in the following equation:

$$\text{therapeutic dose} = \frac{\text{Activity Hours}}{\text{Residence time}} \times \frac{\text{desired total body dose}}{\text{maximum tolerated dose.}}$$

20. (Amended) A method of establishing a patient-specific optimally effective dose for administration of a radiopharmaceutical to a patient, the method comprising:

determining a clearance profile for the radiopharmaceutical or a radiopharmaceutical analog, said clearance profile providing a minimum number of time points for determination of the patient-specific residence time of the radiopharmaceutical or the radiopharmaceutical analog,

determining the desired total body dose (TBD) of the radiopharmaceutical for the patient;

determining the patient's mass (M) and maximum effective mass (MEM);

selecting the lower of the patient's mass and maximum effective mass (M or MEM);

determining activity hours (AH) for the radiopharmaceutical or a radiopharmaceutical analog by reference to Equation I:

$$AH = \frac{TBD \times (M \text{ or } MEM)}{\left[\sum_{elec} \Delta_{elect} + \sum_{phot} \Delta_{phot}\, \phi^{TB}_{phot}\right]}$$

(Equation I)

where $\left[\sum_{elec} \Delta_{elect} + \sum_{phot} \Delta_{phot}\, \phi^{TB}_{phot}\right]$

in Equation I represents the sum of electron energy and photon energy deposited in the total body of the patient by the radiopharmaceutical or radiopharmaceutical analog;

determining the patient-specific residence time of an administered tracer dose of the radiopharmaceutical or the radiopharmaceutical analog in the whole body of the patient;

and

establishing a therapeutic dose of the radiopharmaceutical for the patient by dividing the activity hours by the patient-specific residence time to obtain a value and optionally multiplying the value by an attenuation factor, said attenuation factor being determined by the TBD divided by the maximum tolerated dose for the radiopharmaceutical.

84. (Amended) The [method] optimally effective patient-specific therapeutic dose of claim 19 wherein the radiopharmaceutical is an ^{131}I-labeled anti-B1 antibody.